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(21) International Application Number: PCT/GB97/01502 (22) International Filing Date: 3 June 1997 (03.06.97) (30) Priority Data: 9616237.5 1 August 1996 (01.08.96) GB (71) Applicant (for all designated States except US): NORTON HEALTHCARE LIMITED [GB/GB]; Gemini House, Flex Meadow, Harlow, Essex CM29 5TJ (GB). (72) Inventor; and (75) Inventor/Applicant (for US only): MILLER, Fiona [GB/GB]; Norton Healthcare Limited, Gemini House, Flex Meadow, Harlow, Essex CM29 5TJ (GB). (74) Agent: PAWLYN, Anthony, Neil; Urquhart-Dykes & Lord, Tower House, Merriion Way, Leeds LS2 8PA (GB).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: AEROSOL FORMULATIONS (57) Abstract The replacement of chlorofluorohydrocarbon propellants in medical aerosols is of the utmost importance to the pharmaceutical industry. A number of formulations have been investigated. The present invention provides a medical aerosol formulation comprising a particular medicament, a fluorocarbon propellant and 6 to 25 % w/w of the total formulation of a polar co-solvent, such formulation being substantially free of surfactant. Cannisters suitable for delivering such a pharmaceutical formulation are also provided.		

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AEROSOL FORMULATIONS

This invention relates to pharmaceutical formulations for inhalation aerosols. The Montreal Protocol on ozone depleting gases has made the reformulation of existing pharmaceutical aerosols for inhalation treatment containing chlorofluorohydrocarbon propellants, a matter of urgency for the pharmaceutical industry.

A number of hydrofluorocarbons (HFCs) have been the subject to toxicological testing and two in particular P134a (1,1,1,2-tetrafluoroethane) and P227 (1,1,1,2,3,3,3-heptafluoropropane) have been identified as safe for use in pharmaceutical aerosols.

A number of patent applications have been submitted in this field, the first being EP 372777, which discloses the use of four component mixtures, comprising a medicament, a surfactant, P134a and a co-solvent of higher polarity than the P134a, in the form of a solution or a suspension.

As inhalation aerosols are meant for administration to the lung, it has long been accepted that such formulations should contain as few ingredients as possible, to avoid putting unnecessary materials into the lung.

Historically, despite EP 372777, solution aerosols contained only medicament, propellant or propellant mixtures and, if necessary, co-solvent, usually ethanol, eg US 2868691. The use of a surfactant was normally unnecessary for solution aerosols. However, historically medicinal suspension aerosols have contained a surfactant eg US 3014844, as it was considered that the use of a surfactant was necessary to prevent agglomeration of particles, to prevent adhesion to the sides of the canister, and to aid valve lubrication and prevent valve sticking.

However it was disclosed in EP 616525 that it is possible to prepare medicament suspensions in a hydrofluorocarbon without the need for a surfactant, if a polar co-solvent was added. The normal co-solvent ethanol, has well established

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physiological actions and being a pure absorbable liquid eliminates any possibility of residues remaining in the lung. Irritation or possible toxicity from the surfactant, many of which are mixtures of similar compounds, are avoided.

EP 616525 specifically limits the polar co-solvent level to 0.01 to 5% w/w and in particular states (page 3, line 55) that the preferred level is about 0.1% w/w.

According to a first aspect of the present invention there is provided a medicinal aerosol formulation comprising a particulate medicament, a fluorocarbon propellant and 6% to 25% w/w of the total formulation of a polar co-solvent, such formulation being substantially free of surfactant.

According to a second aspect of the present invention there is provided a medicinal aerosol formulation, comprising one or more particulate medicaments, one or more fluorocarbon or hydrocarbon or aliphatic gas propellants and 6% to 25% w/w of a polar co-solvent.

According to a third aspect of the present invention there is provided a canister suitable for delivering a pharmaceutical aerosol formulation, which comprises a container capable of withstanding the vapour pressure of the propellant used, which container is closed with a metering valve and contains a pharmaceutical aerosol formulation which comprises particulate medicament, a propellant consisting all or part of fluorocarbon and 6% to 25% of a polar co-solvent, which is substantially free of surfactant.

It has now been surprisingly found that higher levels of alcohol have beneficial results. Levels of 6% or more of ethanol produce satisfactory suspensions, which do not agglomerate on standing, and on reshaking produce finely dispersed medicament. It is believed that the higher levels of alcohol reduce the degree of deposition on the inside of the can. This is a very desirable feature. In addition, the use of these larger percentages of ethanol enables a much cheaper production process.

Medicinal aerosols can be filled either with one dose of liquid containing all of the ingredients mixed together or by

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a two dose process where the first dose contains the medicament and all other ingredients, including co-solvents, surfactants, if any, ancillary compounds eg flavours, if any, and some times some of the propellant followed by a second dose of pure propellant. This two dose fill has major cost advantages in that the volume of mix for a fixed number of cans is significantly smaller enabling the use of smaller mixing vessels. In particular, with the use of the new HFC propellants, which have lower boiling points than the old CFC propellants, the use of a one dose fill may involve the use of cooled pressurised vessels to prevent evaporation of the propellant gas during mixing and filling. With the new formulations with added extra co-solvent a first mix of just medicament suspended in the co-solvent can be used, followed by a second dose of pure propellant. This means that the propellant can be dosed directly from a holding tank into the can without any need to mix and store with the other ingredients. For example a mix weight of 1g of medicament and co-solvent can be followed by 7.5g of propellant. In this way the volume to be mixed is reduced from 8.5g to 1g. All the examples in EP 616525 are of laboratory scale, where the handling problems are much easier, but all the formulations described are such that it would not be practicable to fill in two doses without mixing the propellant, as is the case with the present disclosure.

The description of the filling method given on page 5 lines 2-13 indicates that only a one dose filling method is envisaged.

In all cases of the present invention the medicament consists of a particle size suitable for inhalation into the lung and will thus be less than 100 microns, desirably less than 20 microns and preferably in the range of 1-10 microns, normally with a mean particle size 1-5 microns.

Medicaments which may be administered in aerosol formulations according to the invention include any drug useful in inhalation therapy which may be presented in a form which is substantially completely insoluble in the selected propellant.

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Appropriate medicaments may thus be selected from, for example, analgesics, eg codeine, dihydromorphine, ergotamine, fentanyl or morphine; anginal preparations, eg diltiazem; antiallergics, eg cromoglycate, ketotifen or nedocromil; anti-infectives, eg cephalosporins, penicillins, streptomycin, sulphonamides, tetracyclines and pentamidine; antihistamines, eg methapyrilene; anti-inflammatories, eg beclomethasone, flunisolide, budesonide, tipredane, triamcinolone acetonide or fluticasone; antitussives, eg noscapine; bronchodilators, eg ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropanolamine, pirbuterol, reproterol, rimiterol, salbutamol, salmeterol, terbutaline, isoetharine, tolubuterol, orciprenaline; diuretics, eg amiloride; anticholinergics, eg ipratropium, atropine or oxitropium; hormones, eg cortisone, hydrocortisone or prednisolone; xanthines, eg aminophylline, choline theophyllinate, lysine theophyllinate or theophylline; and therapeutic proteins and peptides, eg insulin or glucagon. It will be clear to a person skilled in the art that, where appropriate, the medicaments may be used in the form of salts (eg as alkali metal or amine salts or as acid addition salts) or as esters (eg lower alkyl esters) or as solvates (eg hydrates) to optimise the activity and/or stability of the medicament and/or to minimise the solubility of the medicament in the propellant.

Preferred are those compounds which are also substantially insoluble in the co-solvent. Particularly preferred as medicament is salbutamol either as base or as a salt and especially salbutamol sulphate.

Co-solvents may be selected from polar alcohols and polyols, particularly C₂-C₆ aliphatic alcohols and polyols, such as propylene glycol, and preferably ethanol. Levels of co-solvent will be between 6% and 25% w/w of the total canister content, preferably between 10-15% w/w of canister content.

The propellant may be a hydrofluorocarbon, particularly P134a or P227. Other hydrofluorocarbons or hydrocarbons or aliphatic gases (eg Dimethylether) may be added to modify the

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propellant characteristics as required.

The product is preferentially produced by weighing the active medicament and suspending it in the co-solvent. The appropriate amount of suspension is then dosed into the can, followed by a second dose of propellant or propellant mix. However, a one shot fill or any other equivalent method may be employed.

The normal medicinal product on the market has an actuator with spray orifice diameter of about 480 microns. However, with the larger percentages of ethanol envisaged in this invention, it is desirable that the co-solvent evaporates from the particles as rapidly as possible.

This is achieved by reducing the aperture to between 100-300 microns, which for the same dosage or drug, gives more rapid evaporation of the co-solvent. A particularly preferred embodiment of the invention is a combination of a level 10-15% co-solvent (normally ethanol) with a stem aperture of 150-250 microns.

The invention is further described by means of example but not in any limitative sense.

Example

Salbutamol Sulphate	0.03g
Ethanol	0.97g
Tetrafluoroethane (P134a)	7.5g

The salbutamol sulphate previously micronised to give over 90% of particles below 10 microns was weighed out and added to the ethanol. The suspension was mixed until it was smooth and uniform and then filled into the aerosol canister. The metering valve assembly was crimped (preferably vacuum crimped) on the canister and then the P134a was filled through the valve. The valve capacity is such as to deliver 100 micrograms of salbutamol, as salbutamol sulphate per actuation.

A particularly preferred use of such a canister is in a patient breath operated device rather than the normal hand

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operated device. Such devices are available commercially such as those under the trade mark "Easi-Breathe".

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Claims:

1. A medicinal aerosol formulation comprising a particulate medicament, a fluorocarbon propellant and 6% to 25% w/w of the total formulation of a polar co-solvent, such formulation being substantially free of surfactant.
2. A medicinal aerosol formulation, comprising one or more particulate medicaments, one or more fluorocarbon or hydrocarbon or aliphatic gas propellants and 6% to 25% w/w of a polar co-solvent.
3. A formulation as claimed in claim 1 or claim 2, wherein the medicament is an anti-allergic, a bronchodilator or an anti-inflammatory steroid.
4. A formulation as claimed in claim 3, where the medicament is ephedrine, adrenaline, fenoterol, formoterol, isoprenaline, metaproterenol, phenylephrine, phenylpropandamine, pirbuterol, reproterol, rimiterol, terbutaline, isoetharine, orciprenaline, salbutamol, salmeterol, sodium cromoglycate, fluticasone, beclomethasone or similar molecule and any physiologically acceptable salt, solvate or ester of such compound.
5. A formulation, as claimed in claims 1-3, where the medicament is a salt of salbutamol.
6. A formulation, as claimed in claims 1-3, where the medicament is a salt of formoterol (sometimes called eformoterol).
7. A formulation according to any of claims 1 to 5, wherein the propellant is 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoro-n-propane.
8. A formulation according to any of claims 1 to 5,

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where the co-solvent level is 10-15%.

9. A formulation according to any of claims 1-5, wherein the polar co-solvent is ethanol.

10. A canister suitable for delivering a pharmaceutical aerosol formulation, which comprises a container capable of withstanding the vapour pressure of the propellant used, which container is closed with a metering valve and contains a pharmaceutical aerosol formulation which comprises particulate medicament, a propellant consisting all or part of fluorocarbon and 6% to 25% of a polar co-solvent, which is substantially free of surfactant.

11. A canister according to claim 9, fitted into an adaptor with an aperture of 100-300 microns.

12. A product according to claims 9 and 10 where the medicament is as per claim 4.

13. A product according to claims 9-11, where the medicament is a salt of salbutamol.

14. A product according to claims 9-11, where the medicament is a salt of formoterol.

15. A canister according to claims 9 and 10, which is actuated by a breath operated device.

16. A product according to claim 15, where the medicament is a salt of salbutamol.

17. A product according to claim 15, where the medicament is a salt of formoterol.

INTERNATIONAL SEARCH REPORT

Intern 11 Application No
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A. CLASSIFICATION OF SUBJECT MATTER

A 61 K 9/12

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO, A, 93/11 745 (GLAXO GROUP LIMITED) 24 June 1993 (24.06.93), abstract; claims 1-15. --	1-5, 7-10
A	WO, A, 93/11 743 (GLAXO GROUP LIMITED) 24 June 1993 (24.06.93), abstract; claims 1-21. --	1-5, 7-10
A	WO, A, 94/03 153 (GLAXO GROUP LIMITED) 17 February 1994 (17.02.94), abstract; claims 1-12. --	1-5, 7-10
A	WO, A, 94/13 262 (JAGER et al.) 23 June 1994 (23.06.94), abstract; claims 1-38,	1-5, 7-9

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	<p>especially claim 4.</p> <p>-----</p>	

ANHANG

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ANNEX

to the International Search
Report to the International Patent
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ANNEXE

au rapport de recherche inter-
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WO A1 9311745		AP A0 9200461 AT E 1283500 AU A1 6085079 AU A1 6085179 AU A1 6085279 AU B2 6639044 AU B2 6639055 AU B2 6639066 CN A 1075075 CN A 1075079 CN A 1075080 CN A 1075081 CN A 1075082 CN A 1075083 CN A 1075084 CN A 1075085 CN A 1075086 CN A 1075087 CN A 1075088 CN A 1075089 CN A 1075090 CN A 1075091 CN A 1075092 CN A 1075093 CN A 1075094 CN A 1075095 CN A 1075096 CN A 1075097 CN A 1075098 CN A 1075099 CN A 1075100 CN A 1075101 CN A 1075102 CN A 1075103 CN A 1075104 CN A 1075105 CN A 1075106 CN A 1075107 CN A 1075108 CN A 1075109 CN A 1075110 CN A 1075111 CN A 1075112 CN A 1075113 CN A 1075114 CN A 1075115 CN A 1075116 CN A 1075117 CN A 1075118 CN A 1075119 CN A 1075120 CN A 1075121 CN A 1075122 CN A 1075123 CN A 1075124 CN A 1075125 CN A 1075126 CN A 1075127 CN A 1075128 CN A 1075129 CN A 1075130 CN A 1075131 CN A 1075132 CN A 1075133 CN A 1075134 CN A 1075135 CN A 1075136 CN A 1075137 CN A 1075138 CN A 1075139 CN A 1075140 CN A 1075141 CN A 1075142 CN A 1075143 CN A 1075144 CN 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